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Chemical Category
BENZENE 1,1'-METHYLENEBIS[4-ISOCYANATO- (101-68-8)

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A 02

OFFICE OF TOXIC SUBSTANCES

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401 M Street, SW
Washington, DC 20460

MR 25385

Attn: 8(d) HEALTH & SAFETY STUDY REPORTING RULE
(REPORTING)

Dear Sir/Madam:

We herewith submit a copy of the following recently completed health and safety study: "MDI: Study of absorption after single dermal and intradermal administration in rats."

Name of chemical substance: 1,1' –methylenebis [4-isocyanato-	Benzene
Common Name	Monomeric MDI
Chemical Abstracts Service Number	101-68-8
Abrreviation:	4,4' – MDI
Authors:	E. Leibold, H.D. Hoffmann, B. Hildebrand BASF Aktiengesellschaft, Ludwigshafen, Germany

The International Isocyanate Institute (III) project identification number (11341) has been marked on the title page of the report. Please refer to the III identification number in any communication regarding this study. The enclosed report does not contain any Confidential Business Information.

This study was sponsored by the International Isocyanate Institute on behalf of the following:

BASF Corporation
Bayer Corporation
Dow Chemical Company
Huntsman Polyurethanes
Lyondell

Contain NO CBI

Sincerely,

M.J. Blankenship
Managing Director

cc: J. Chapman
D. Gilbert
J. Jadlocki
J. Lyon
T. Landry
R. Robert
M. Spence

III Project 126

III ref. 11341

MDI: Study of absorption after single dermal and intradermal administration in rats

Authors

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III Report

International Isocyanate Institute Inc.

The Scientific Office, Bridgewater House, Whitworth Street, Manchester M1 6LT.

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1b0150

REPORT

^{14}C-Methylenebisphenylisocyanate (^{14}C-MDI) - Study of the Absorption after Single Dermal and Intradermal Administration in Rats

AUTHORS

Dr. E. Leibold (Study Director)
Dr. H.D. Hoffmann
Dr. B. Hildebrand

STUDY COMPLETED ON

June 7, 1999

PERFORMING LABORATORY

Department of Toxicology of
BASF Aktiengesellschaft
67056 Ludwigshafen/Rhein, FRG

LABORATORY PROJECT IDENTIFICATION

01B0431/946010

STUDY SPONSOR

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201 Main Street
La Crosse, WI 54601
USA

This report consists of 39 pages.

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SPONSOR S PROJECT NO.: 126-EU-MTX

GLP STATEMENT

Study Title: Report: ^{14}C-Methylenebisphenylisocyanate (^{14}C-MDI) - Study of the Absorption after Single Dermal and Intradermal Administration in Rats

Project number: 01B0431/946010

This study was conducted in accordance with the GLP-provisions of the "Chemikaliengesetz" (Chemicals Act; Bundesgesetzblatt 1994, Teil I, 29.07.1994; FR Germany) and with the "OECD Principles of Good Laboratory Practice (Paris, 1981).

E. Leibold June 7, 1999

Dr. rer.nat. E. Leibold
(Study Director)

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10

STATEMENT

of the Quality Assurance Unit

Number of test substance: 94/431

Name of test substance: ^{14}C-Methylenbisphenylisocyanate

Study Title: Report: ^{14}C-Methylenbisphenylisocyanate (^{14}C-MDI) - Study of the Absorption after Single Dermal and Intradermal Administration in Rats

The Quality Assurance Unit inspected the study, audited the final report, and reported findings to the Study Director and to Management.

Phase of study/ inspection	Date of inspection	Report to Study Director and to Management
Protocol:	Jan. 13, 1995	May 06, 1997
Conduct of study:	April 30, 1997 May 05, 1997 Dec. 05, 1997 Dec. 12, 1997	May 06, 1997 May 06, 1997 Dec. 08, 1997 Dec. 12, 1997
Audit of the report:	Nov. 17, 1998	Nov. 17, 1998

Remark: Parts of analytics were inspected independently by the Quality Assurance Unit of the respective analytical laboratory.

Ludwigshafen, April 20, 1999

H. Hajok
(Head of Quality Assurance Unit)

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1 SUMMARY

The absorption, distribution and excretion of radioactivity was studied in groups of four male Wistar rats following a single dermal and intradermal administration of ^{14}C-Methylenebisphenylisocyanate (^{14}C-MDI) at nominal dose levels of 4.0 and 0.4 mg/cm² for dermal administration and 0.4 mg/animal for intradermal administration. These dose levels nominally corresponded to 40 and 4.0 mg/animal for dermal administration. Considering the animal weights, dose levels corresponded to about 140 and 14 mg/kg body weight (dermal administration) and 1.4 mg/kg body weight (intradermal administration). In the experiments with dermal administration, animals were exposed for 8 hours and sacrificed 8, 24 or 120 h after beginning of exposure. In the experiment with intradermal administration, animals were sacrificed 120 h after treatment.

After dermal administration of ^{14}C-MDI, mean recoveries of radioactivity from all dose groups were in the range from 97.86 to 108.07 % of the total radioactivity administered. Generally, the largest proportion of radioactivity was found at the application site and dressing.
The total amount of radioactivity absorbed (including excreta, cage wash, tissues/organs and carcass) increased with increasing sacrifice time. Dermal absorption was very low and quantitatively similar at both dose levels; maximally ca. 0.9 % of the applied radioactivity was absorbed.

After intradermal administration of ^{14}C-MDI, the mean recovery of radioactivity was 100.90 % of the radioactivity administered. The largest proportion of radioactivity was found at the application site. The total amount of radioactivity absorbed (including excreta, cage wash, tissues/organs and carcass) amounted to about 26 % of the radioactivity applied.

These results are summarized in the table below:

Percentage of radioactivity absorbed and total amount of radioactive material absorbed

Exposure time [h]	Sacrifice time [h]	dermal: 4.0 mg/cm²	dermal: 0.4 mg/cm²	intradermal: 0.4 mg/animal
		% abs.	% abs.	% abs.
8	8	0.21	0.14	25.87
8	24	0.66	0.23	
8	120	0.88	0.69	

Irrespective of the mode of administration of ^{14}C-MDI, concentrations of radioactivity in tissues and organs generally were below 1 µg Eq/g at 120 h after administration.
In summary, the results of this study comparing systemic availability of radioactivity after single dermal and intradermal administration of ^{14}C-MDI clearly demonstrated very limited absorption after dermal administration but considerable absorption after intradermal administration. The radioactivity absorbed was distributed in all organs and tissues with highest levels being found in carcass, thyroid, muscle, plasma and liver. Excretion of radioactivity mainly occurred via the feces.

2 INTRODUCTION

Methylenebisphenylisocyanate (MDI) is an aromatic diisocyanate which is widely used in the manufacture of polyurethanes.
Generally, information on the dermal absorption and excretion can aid in the interpretation of test results from other toxicological studies and in the extrapolation of data from animals to man for risk assessment purposes.

The study had the following objectives:

- To determine the absorption, distribution and excretion of radiolabelled products after a single dermal and intradermal administration of ^{14}C-Methylenebisphenylisocyanate (^{14}C-MDI) diluted in acetone (dermal administration) or corn oil (intradermal administration) as a function of time and dose to male rats.

3 MATERIAL AND METHODS

3.1 Test Guidelines

The study was performed according to the following guideline:

- U.S. EPA, Health Effects Test Guidelines, OPPTS 870.7600, Dermal Penetration, "Public Draft" dated June 1996

3.2 Time schedule

Start of experiments:	30 April 1997
Completion of experiments:	03 August 1998

3.3 Test substance

3.3.1 ^{14}C-labelled material

Name:	^{14}C-Methylenebisphenylisocyanate
Abbreviation:	^{14}C-MDI
Chemical name:	4,4'-Methylenebis-[ring-U-^{14}C]-phenylisocyanate
ZHT test substance No.:	94/431
Molecular formula:	$C_{15}H_{10}N_2O_2$
Origin:	supplied by the sponsor; purified by the Isotope Laboratory of BASF Aktiengesellschaft, Ludwigshafen, Germany
Batch/Lot No.:	588-02 and 588-1201
Radiochemical purity:	> 95 %; checked prior to all experiments (see also Purity Statements in Appendix)
Physical state:	solid
Storage:	in refrigerator and in the dark

3.3.2 unlabelled material

Name:	Lupranat ME
Chemical name:	4,4'-Methylenebis-phenylisocyanate

Abbreviation:	MDI
Origin:	Elastogran GmbH, Ludwigshafen, Germany
Batch/Lot No.:	152.08.16.95
ZHT test substance No.:	96/490-1
Chemical purity:	> 95 % (confirmed by re-analysis in August 1998)
Physical state:	Solid
Storage:	refrigerator

The analyses of the test substances were carried out at BASF Aktiengesellschaft, Ludwigshafen, FRG.

3.3.3 Vehicle

For the dermal administration, dried acetone was used as vehicle.
For the intradermal administration, corn oil was used as vehicle.

3.3.4 Stability and homogeneity of the test substance preparation

Stability in vehicle:	verified in all experiments (see raw data for details)
Homogeneity and correctness of the concentrations:	verified analytically in all experiments (see raw data for details)

The analyses of the test substance preparations were carried out by the Bioanalytical Laboratory of the Department of Toxicology of BASF Aktiengesellschaft, Ludwigshafen, FRG.

3.4 HPLC Analysis of radiochemical purity

The radiochemical purity of the application solutions of ^{14}C-MDI was checked by HPLC analysis.

Column:	Nucleosil 120, 5C18, 250 x 4 mm
Mobile phase:	Acetonitrile + 0.01 M Trifluoroacetic acid
Flow rate:	0.6 - 1.2 ml/min
Sample volume:	1-5 µl
Detection:	[illegible] nm
	HPLC Radioactivity Monitor LB 506 C
	Cell YG 150 U4D

3.5 Preparation of test substance

3.5.1 Material for dermal administration

Stock solutions were prepared for the labelled material in dried acetone. Unlabelled material was given to appropriate aliquots of the acetone solution in order to achieve the required specific activity and test substance concentration. Before start of and at the end of the administrations samples were taken to check the amount of radioactivity in the solution and to demonstrate the stability and homogeneity.

3.5.2 Material for intradermal administration

Stock solutions were prepared for the labelled material in dried acetone. Unlabelled material was added to appropriate aliquots of the acetone solution in order to achieve the required specific activity. The organic solvent was evaporated to dryness at 30° C under vacuum. In order to achieve the nominal concentration of the test substance preparation the carrier (corn oil) was added to the remaining material. Prior to administration the solution was stirred and sonicated in order to produce a homogeneous preparation. Before start of and at the end of the administrations samples were taken to determine the amount of radioactivity in the solution and to demonstrate the homogeneity.

Any detail with respect to the various doses and amounts of radioactivity is documented in the study raw data.

3.6 Test system

Animals:	Wistar rats
Strains:	Chbb:THOM (SPF)
Origin:	Dr. Karl Thomae, Biberach a.d. Riss (FRG)
Sex:	Male
Age:	about 8 weeks at application (pretest animals: about 15 weeks)
Weight:	ca. 250-300 g (weight was measured prior to dosing and is recorded in the study raw data; see also tables 4-6; 8-11)
Rationale:	Recognized by international guidelines as the recommended test system. Study results will be used in relation to already available data from the same test system.

- Husbandry

Room:	Animals were kept under conventional hygienic conditions in an air-conditioned room at 20-24° C and 30-70 % relative humidity. These parameters are maintained under central control. Deviations from these ranges did not occur.
Identification, Caging:	During acclimatization and prior to the experiment each two animals in type III Macrolon cages; during experiments individually in all-glass metabolism cages; type Metabowl (Jencons, Leighton Buzzard, UK) which were labelled with the project number and the animal number.
Diet:	Kliba lab diet for rat-mouse-hamster either pelletized (e.g. during acclimatization) or granulated (e.g. in metabolism cages). Ad libitum prior to and during the experiment. Origin: Klingentalmühle AG, CH-4303 Kaiseraugst, Switzerland
Water:	Tap water ad libitum
Analysis of diet:	The feed used in the study was assayed for chemical and microbiological contaminants. In view of the aim and duration of this study, contaminants occurring in commercial feed are unlikely to influence the results of the study.
Analysis of water:	The drinking water is regularly assayed for chemical contaminants by the municipal authorities of Frankenthal and the Technical Services of BASF Aktiengesellschaft as well as for germ cell by a contract laboratory. In view of the aim and duration of the study there are no special requirements exceeding the specifications of drinking water.
Selection of animals:	Animals were assigned to the groups randomly.
Health status and clinical examinations:	The health status of the animals was checked prior to and during the experiment at least once daily at work days.

3.7 Dose selection, dose groups

3.7.1 Doses and dose groups

dermal administration:	high dose:	4 mg/cm²
	low dose:	0.4 mg/cm²
intradermal administration:		0.4 mg/animal

Experiments were performed with groups of 4 animals per dose and exposure period.

3.7.2 Rationale for dose selection

These dose levels have been selected in accordance with the investigations carried out by Rattray et al. (Toxicology 88, 15-30, 1994) and Vock & Lutz (Toxicol. Letters 92, 93-100, 1997) so that the results given therein could be set in relation to the results of that study.

3.8 Administration of test material

3.8.1 Dermal administration

Twenty-four hours prior to dosing the back shoulders of the rats were clipped free of hair and the area (about 10 cm²) was washed with acetone. A silicon ring was glued to the skin, the test substance preparation (about 10 µl/cm²) was administered with a syringe which was weighed before and after application (glue: Histoacryl®; B. Braun, Melsungen, Germany). A nylon mesh gauze was then glued to the surface of the silicone ring and a porous bandage used to encircle the trunk of the animal.

3.8.2 Intradermal administration

Twenty-four hours prior to dosing the back shoulders of the rats were clipped free of hair and the area (about 10 cm²) was washed with acetone. The test substance preparation (about 100 µl) was administered with a syringe which was weighed before and after application. The injection area was sealed with tissue glue (Histoacryl®; B. Braun, Melsungen, Germany) in order to avoid leakage of the test substance preparation.

3.9 Study design

3.9.1 Pretest for intradermal administration

Allthough doses were set in relation to existing toxicity data, it could not be ruled out entirely, that animals used in this study would show unexpected symptome especially after intradermal administration. Therefore, a pretest with unlabelled test substance was performed in two male rats with intradermal administration of 0.4 mg MDI/animal.

3.9.2 Balance/Excretion (dermal; intradermal administration)

In this set of experiments, animals were dosed and then placed in metabolism cages in order to collect excreta after 8, 24, 48, 72, 96 and 120 h if animals were not sacrificed before. After the respective exposure period the protective cover was removed and the exposed skin was washed with a mild soap solution. At the end of the various collection periods animals were sacrificed and the following specimens/tissues were analysed for remaining radioactivity:

excreta, bloodcells, plasma, lung, heart, spleen, kidneys, adrenals, gonads, muscle, brain, adipose tissue, bone, thyroid, pancreas, stomach contents, stomach, gut contents, gut, liver, carcass, skin [treated (= application site) and non-treated areas (surrounding skin)]

For balance estimates the cage wash and skin wash as well as the protective cover (including the silicone ring) were also analysed for radioactivity.

3.9.2.1 Experiment 1

animals: 12 males
dosing: 4.0 mg/cm² (high dose); dermal

Exposure regime

Duration of exposure [h]	8		
Sacrifice after [h]	8	24	120
number of animals	4	4	4

3.9.2.2 Experiment 2

animals: 12 males
dosing: 0.4 mg/cm² (low dose); dermal
Exposure regime

Duration of exposure [h]	8		
Sacrifice after [h]	8	24	120
number of animals	4	4	4

Note: Since skin penetration and consequently tissue levels of radioactivity were very low in Exp. 1, radioactivity was only determined in the following samples:
excreta, plasma, carcass, skin [treated (= application site) and non-treated areas (surrounding skin)], skin wash, cage wash.

3.9.2.3 Experiment 3

animals: 4 males
dosing: 0.4 mg/animal; intradermal
Exposure regime: sacrifice: 120 h after administration

3.9.3 Sampling of blood serum after dermal and intradermal administration of non-radioactive MDI

In order to get samples for immunological investigations, the following experiments were be performed at the request of the sponsor:

Animals were treated and then placed in steel wire mesh cages. Blood samples were taken retroorbitally and serum will be prepared from these blood samples which will be used for immunological investigations.

3.9.3.1 Experiment 4

Number of animals: 15 male animals
Dosing: 4 mg/cm² dermal (day 0)
(10 µl/cm²; treatment area: 10 cm²)
Test substance: non-radioactive MDI

Treatment and sampling regime:

Duration of exposure	8 h	21 days (no skin wash after 8 h)
Number of animals	10	5
Blood sampling	Day -1 Day 7 Day 14 Day 21	Day -1 Day 7 Day 14 Day 21

3.9.3.2 Experiment 5

Number of animals: 10 male animals
Dosing: 0.4 mg/animal, intradermal (day 0)
Test substance: non-radioactive MDI

Sampling regime:

Number of animals	10
Blood sampling	Day -1 Day 7 Day 14 Day 21

Details of these experiments are recorded in the raw data and will not be reported. The results of the immunological investigations are reported elsewhere.

3.10 Analysis and Measurements

In order to collect urine and feces the animals were individually placed in all-glass metabolism cages immediately after treatment.

3.10.1 Preparation of samples and measurement of radioactivity

Details of such procedures are described in the Standard Operation Procedures; therefore only a brief description of the relevant steps is given in the following.

Aliquots of liquid samples (plasma, urine, skin wash, cage wash) were mixed with scintillation cocktail (Hionic Fluor, Packard) and analyzed for radioactivity without any additional treatment.
Feces were suspended in distilled water. The carcass was homogenized with distilled water using a WARING Blendor. Aliquots of these suspensions were dried by lyophilization in a freeze dryer (LYOVAC GT 3).
Aliquots of the remaining powder and of the homogenate of the other tissues or aliquots of the skin were solubilized in SOLUENE (Packard). In order to bleach these samples isopropanol and H_2O_2-solution were added and left for 24 hours at room temperature. After addition of scintillation cocktail the samples were counted for 10 min in a liquid scintillation counter (LSC; Wallac type 1409) and the disintegration rate corrected by the respective background. The limit of detection was taken as twice the background disintegration rate.

3.11 Data processing

Tables presented in the report are computer generated. The group mean and individual data are rounded appropriately for inclusion in the report. As a consequence, calculation of group mean data from the individual data presented in the report will in some instances, yield a minor variation in value.

3.11.1 Calculations

Depending on the preparation of the samples the appropriate formulas were chosen. Calculations were performed using formula I and III (see below) for all these samples which were dried by freeze drying technic. The results for the other samples were obtained using formula II and IV (see below).

Key of abbreviations		dimension
DPM	= disintegrations per minute	[DPM]
LSC	= weight of LSC sample	[g]
SOL	= weight of soluene	[g]
FRE	= weight of freeze drying sample	[g]
SAM	= weight of organs/Tissue	[g]
AQU	= weight of Aqua bidest.	[g]
ACT	= specific activity of test material	[DPM/µg]
EQUTIS	= equivalents of test material per tissue weight	[µg/g]
D_{rad}	= dose of radioactivity administered	[DPM]

Formula I

$$\% \ of \ D_{rad} = \frac{\sum_{n=1}^{n} DPM_n \ / \ LSC_n}{n} \times \frac{SOL}{FRE} \times (\ SAM + AQU \ ) \times \frac{100}{D_{rad}}$$

Formula II

$$\% \ of \ D_{rad} = \frac{\sum_{n=1}^{n} DPM_n \ / \ LSC_n}{n} \times (\ SAM + AQU \ ) \times \frac{100}{D_{rad}}$$

Formula III

$$EQUTIS = \frac{\sum_{n=1}^{n} DPM_n \ / \ LSC_n}{n} \times \frac{SOL}{FRE} \times \frac{SAM + AQU}{SAM \times ACT}$$

Formula IV

$$EQUTIS = \frac{\sum_{n=1}^{n} DPM_n \,/\, LSC_n}{n} \times \frac{SAM + AQU}{SAM \times ACT}$$

Material absorbed:

The total amount of test compound that was absorbed by each animal is the sum of the quantity found in the excreta (urine, feces), organs/tissues, carcass and cage wash.

3.12 Retention of Records

The original of the study protocol, report and raw data are stored at BASF Aktiengesellschaft for at least the period of time specified in the GLP regulations. Details concerning responsibilities or locations of archiving can be seen from the respective SOPs and from the raw data. The specimens were retained until finalization of the report. The official regulations concerning radioactive specimens have been taken into account.

4 RESULTS and DISCUSSION

4.1 Stability, homogeneity of the application solution

Based on the results of the analyses, the application solutions were found to be homogeneous and the test substance was stable in the respective carriers.

4.2 Excretion, retention and tissue concentrations after dermal application of ^{14}C-MDI

Summarized data and single animal data which are discussed in the following sections are presented in tables 1-2 and 4-10.

Mean values of the amounts of excreted and residual radioactivity after a single dermal administration of ^{14}C-MDI in acetone to male rats at nominal dose levels of 4.0 and 0.4 mg/cm² (corresponding to 40.0 and 4.0 mg/animal) are presented in tables 1-2. Considering the animal weights, dose levels corresponded to about 140 and 14 mg/kg body weight.
The corresponding single animal data are included in tables 4-10.

4.2.1 High dose
(Tables 1, 4-7)

Following a single dermal administration of ^{14}C-MDI at a nominal dose level of 4.0 mg/cm² (40.0 mg/animal; ca. 140 mg/kg bw), the mean recovery of radioactivity in the different groups was between 97.86 % and 103.09 % of the applied radioactivity.
In all groups, the largest proportion of radioactivity was generally recovered from the dressing and the skin of the application site. Immediately after an exposure of 8 hours, application sites and dressings contained 29.63 % and 65.93 % of the applied radioactivity, respectively. In the groups sacrificed after 24 hours and 120 hours, 25.49 % and 32.21 % of the applied radioactivity was found at the application site and 64.25 % and 69.15 % was contained in the dressings. The penetration of radioactivity into the skin adjacent to the application site was between 0.55 and 7.14 % of the applied radioactivity. In skin wash, which was performed at the end of the 8 h exposure period, 0.48, 0.32 and 0.31 % of the applied radioactivity was found in the 8, 24 and 120 h groups, respectively.
The amount of radioactivity absorbed (including excreta, cage wash, tissues/organs and carcass) increased from 0.21 % of the dose applied at 8 h after application to 0.66 % at 24 h after application and to 0.88 % at 120 h after application. At the early timepoints (8 and 24 h), the absorbed radioactivity was excreted via urine and feces in similar amounts. After 24 h, excretion via feces was predominant with the rate of excretion being relatively constant over this time period.

The radioactivity absorbed was distributed in all organs and tissues. Due to the limited dermal absorption, concentrations of radioactivity in organs and tissues analyzed were considerably below 1 µg Eq/g except for the 24 h carcass samples. Levels of tissue radioactivity were comparable at 8 and 24 h and declined until 120 h after application with highest levels generally being found in carcass, thyroid, muscle, plasma and liver.

4.2.2 Low dose
(Tables 2, 8-10)

Following a single dermal administration of ^{14}C-MDI at a nominal dose level of 0.4 mg/cm^2 (4.0 mg/animal; ca. 14 mg/kg bw), the mean recovery of radioactivity in the different groups was between 102.87 % and 108.07 % of the applied radioactivity.
In all groups, the largest proportion of radioactivity was generally found in the dressing and the skin of the application site. Immediately after an exposure of 8 hours, application sites and dressings contained 54.26 % and 44.49 % of the applied radioactivity, respectively. In the groups sacrificed after 24 hours and 120 hours, 55.6 % and 61.14 % of the applied radioactivity was found at the application site and 50.03 % and 42.64 % was contained in the dressings. The penetration of radioactivity into the skin adjacent to the application site was between 1.37 and 3.17 % of the applied radioactivity. In skin wash, which was performed at the end of the 8 h exposure period, 0.81, 0.82 and 0.47 % of the applied radioactivity was found in the 8, 24 and 120 h groups, respectively.
The amount of radioactivity absorbed (including excreta, cage wash, tissues/organs and carcass) increased from 0.14 % of the dose applied at 8 h after application to 0.23 % at 24 h after application and to 0.69 % at 120 h after application. At the early timepoints (8 and 24 h), the absorbed radioactivity was excreted via urine and feces in similar amounts. After 120 h, excretion via feces was predominant with the rate of excretion being relatively constant over this time period.
Due to the limited dermal absorption in the high dose groups, concentrations of radioactivity were investigated only in plasma and carcass. Tissue concentrations of radioactivity were very low being below 0.1 µg Eq/g. Plasma levels of radioactivity were comparable at 8 and 24 h and declined until 120 h after application. In the remaining carcass, radioactivity concentrations were highest after 120 h.

4.3 Excretion, retention and tissue concentrations after intradermal application of ^{14}C-MDI

Summarized data and single animal data to be discussed in the following sections are presented in tables 3 and 11-12.

Mean values of the amounts of excreted and residual radioactivity after a single intradermal administration of ^{14}C-MDI in corn oil to male rats at a nominal dose level of 0.4 mg/animal are presented in table 3. Using a mean animal weight of 285 g, this dose level nominally corresponded to about 1.4 mg/kg bw.
The corresponding single animal data are included in tables 11-12.

Following a single intradermal administration of ^{14}C-MDI at a nominal dose level of 0.4 mg/animal (ca. 1.4 mg/kg body weight), the mean recovery of radioactivity in the treated group was 100.90 %. The affected area of the skin was about 1 cm^2.
The largest proportion of radioactivity was found at the application site amounting to 66.45 % of the applied radioactivity. The penetration of radioactivity into the skin adjacent to the application site was 8.47 % of the applied radioactivity. In skin wash, which was performed 120 hours after administration, 0.11 % of the applied radioactivity were found.
The amount of radioactivity absorbed (including excreta, cage wash, tissues/organs and carcass) during the 120 h observation period amounted to 25.87 % of the dose applied. The absorbed radioactivity was excreted mainly via the feces with the rate of excretion being relatively constant over this time period.
Despite the considerable systemic availability of radioactivity after intradermal administration of ^{14}C-labelled MDI, concentrations of radioactivity in organs and tissues at 120 h after administration were rather low being below 1 µg Eq/g.

The results of this study comparing systemic availability of radioactivity after single dermal and intradermal administration of ^{14}C-MDI clearly demonstrated very limited absorption after dermal administration but considerable absorption after intradermal administration. Due to the reactive nature of the test substance, considerable amounts of radioactivity could be found at the application site which could not be washed off.

5 CONCLUSION

Following single dermal administration of ^{14} -MDI diluted in acetone there was very limited systemic absorption amounting to 0.9 % of the dose applied at maximum. After single intradermal administration of ^{14}C-MDI diluted in corn oil, considerable systemic availability occurred amounting to about 26 % of dose.

6 TABLES

Table 1: Mean excretion and retention of radioactivity after a single **dermal administration** of ^{14}C-MDI to rats at **nominal dose** levels of **4.0 mg/cm²** (40 mg/animal).
If not stated otherwise, results expressed as % of the radioactivity administered.

Nominal dose [mg/cm²]	4.0		
Exposure time [h]	8		
Sacrifice time [h]	8	24	120
Actual dose [mg/cm²]	4.628	4.701	4.775
Urine	0.01	0.03	0.05
Feces	0.00	0.02	0.13
Cage wash	0.00	0.00	0.03
Bloodcells	0.00	0.00	0.00
Plasma	0.00	0.00	0.00
Lung	0.00	0.00	0.00
Heart	0.00	0.00	0.00
Spleen	0.00	0.00	0.00
Kidney	0.00	0.00	0.00
Adrenals	0.00	0.00	0.00
Gonads	0.00	0.00	0.00
Muscle	0.00	0.00	0.00
Brain	0.00	0.00	0.00
Adipose Tissue	0.00	0.00	0.00
Bone	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00
Pancreas	0.00	0.00	0.00
Stomach contents	0.00	0.00	0.18
Stomach	0.00	0.00	0.00
Gut contents	0.02	0.02	0.29
Gut	0.00	0.00	0.01
Liver	0.01	0.00	0.00
Carcass	0.17	0.60	0.21
Material absorbed	**0.21**	**0.66**	**0.88**
Skin (surrounding)	4.75	7.14	0.55
Protective cover	65.93	64.25	69.15
Skin (appl. site)	29.63	25.49	32.21
Skin wash	0.48	0.32	0.31
Total recovery	**100.99**	**97.86**	**103.09**
Material absorbed in mg/animal	0.0973	0.3165	0.4299
Material absorbed in mg/cm²	0.0097	0.0316	0.0430

Table 2: Mean excretion and retention of radioactivity after a single **dermal administration** of ^{14}C-MDI to rats at **nominal dose** levels of **0.4 mg/cm²** (4.0 mg/animal).
If not stated otherwise, results expressed as % of the radioactivity administered.

Nominal dose [mg/cm²]	0.4		
Exposure time [h]	8		
Sacrifice time [h]	8	24	120
Actual dose [mg/cm²]	0.419	0.419	0.419
Urine	0.01	0.04	0.09
Feces	0.00	0.05	0.16
Cage wash	0.00	0.01	0.06
Plasma	0.00	0.00	0.00
Carcass	0.13	0.13	0.38
Material absorbed	**0.14**	**0.23**	**0.69**
Skin (surrounding)	3.17	1.37	1.47
Protective cover	44.49	50.03	42.64
Skin (appl. site)	54.26	55.62	61.14
Skin wash	0.81	0.82	0.47
Total recovery	**102.87**	**108.07**	**106.41**
Material absorbed in mg/animal	0.0058	0.0096	0.0290
Material absorbed in mg/cm²	0.00058	0.00096	0.00290

Table 3: Mean excretion and retention of radioactivity after a single **intradermal administration** of ^{14}C-MDI to rats at **a nominal dose** level of **0.4 mg/animal.**
If not stated otherwise, results expressed as % of the radioactivity administered.

Nominal dose [mg/animal]	0.4
Exposure time [h]	8
Sacrifice time [h]	120
Actual dose [mg/animal]	0.515
Urine	4.51
Feces	17.08
Cage wash	0.75
Bloodcells	0.04
Plasma	0.19
Lung	0.03
Heart	0.01
Spleen	0.01
Kidney	0.07
Adrenals	0.00
Gonads	0.04
Muscle	0.01
Brain	0.00
Adipose Tissue	0.00
Bone	0.00
Thyroid	0.00
Pancreas	0.01
Stomach contents	0.05
Stomach	0.02
Gut contents	0.48
Gut	0.09
Liver	0.32
Carcass	2.18
Material absorbed	**25.87**
Skin (surrounding)	8.47
Skin (appl. site)	66.45
Skin wash	0.11
Total recovery	**100.90**
Material absorbed in mg/animal	0.1332

Table 4: Excretion and retention of radioactivity 8 h after a single dermal administration of ^{14}C-MDI to rats at a dose level of 4.0 mg/cm^2.
Single animal data and group mean values, results expressed as % of the radioactivity administered.

Animal No.	1	2	3	4	Mean	SD
Animal weight [g]	269.80	288.90	287.70	286.10	283.13	8.96
Specific acitvity [DPM/mg]	2140624	2140624	2140624	2140624	2140624	—
Dose admin. [mg/kg bw]	130.7	183.1	173.6	164.3	162.9	22.6
Dose admin. [mg/cm²]	3.526	5.289	4.995	4.701	4.628	0.773
Dose admin. [mg/animal]	35.26	52.89	49.95	47.01	46.28	7.73
Radioact. dose [MBq/animal]	1.26	1.89	1.78	1.68	1.65	0.28
Urine 0-8	0.01	0.00	0.01	0.01	0.01	0.01
Subtotal Urine	0.01	0.00	0.01	0.01	0.01	0.01
Feces 0-8	0.00	0.00	0.00	0.01	0.00	0.01
Subtotal Feces	0.00	0.00	0.00	0.01	0.00	0.01
Cage wash	0.00	0.00	0.00	0.00	0.00	0.00
Bloodcells	0.00	0.00	0.00	0.00	0.00	0.00
Plasma	0.00	0.00	0.00	0.00	0.00	0.00
Lung	0.00	0.00	0.00	0.00	0.00	0.00
Heart	0.00	0.00	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00	0.00
Kidneys	0.00	0.00	0.00	0.00	0.00	0.00
Adrenals	0.00	0.00	0.00	0.00	0.00	0.00
Gonads	0.00	0.00	0.00	0.00	0.00	0.00
Muscle	0.00	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.00	0.00	0.00	0.00	0.00
Stomach contents	0.00	0.00	0.00	0.00	0.00	0.00
Stomach	0.00	0.00	0.00	0.00	0.00	0.00
Gut contents	0.02	0.02	0.02	0.02	0.02	0.00
Gut	0.00	0.00	0.00	0.00	0.00	0.00
Liver	0.01	0.01	0.01	0.01	0.01	0.00
Carcass	0.19	0.22	0.18	0.09	0.17	0.06
Percentage absorbed	0.23	0.25	0.22	0.14	0.21	0.05
Surrounding skin	1.33	11.12	1.38	5.15	4.75	4.61
Protective cover	67.97	62.99	61.13	71.63	65.93	4.77
Application site	26.89	29.07	27.15	35.39	29.63	3.96
Skin wash	0.61	0.34	0.41	0.55	0.48	0.12
Total	97.03	103.77	90.29	112.86	100.99	9.64
Material absorbed						
in mg/animal	0.0811	0.1322	0.1099	0.0658	0.0973	0.0296
in mg/cm²	0.0081	0.0132	0.0110	0.0066	0.0097	0.0030

Table 5: Excretion and retention of radioactivity 24 h after a single dermal administration of ^{14}C-MDI to rats at a dose level of 4.0 mg/cm². Single animal data and group mean values, results expressed as % of the radioactivity administered.

Animal No.	5	6	7	8	Mean	SD
Animal weight [g]	274.90	300.50	289.20	276.60	285.30	11.97
Specific acitvity [DPM/mg]	2140624	2140624	2140624	2140624	2140624	---
Dose admin [mg/kg bw]	160.3	156.4	162.6	180.6	165.0	10.7
Dose admin. [mg/cm²]	4.408	4.701	4.701	4.995	4.701	0.240
Dose admin. [mg/animal]	44.08	47.01	47.01	49.95	47.01	2.40
Radioact. dose [MBq/animal]	1.57	1.68	1.68	1.78	1.68	0.09
Urine 0-8	0.01	0.01	0.01	0.01	0.01	0.00
Urine 8-24	0.02	0.02	0.02	0.02	0.02	0.00
Subtotal Urine	0.03	0.03	0.03	0.03	0.03	0.00
Feces 0-8	0.00	0.00	0.00	0.00	0.00	0.00
Feces 8-24	0.01	0.01	0.02	0.02	0.02	0.01
Subtotal Feces	0.01	0.01	0.02	0.02	0.02	0.01
Cage wash	0.00	0.01	0.00	0.00	0.00	0.01
Bloodcells	0.00	0.00	0.00	0.00	0.00	0.00
Plasma	0.00	0.00	0.00	0.00	0.00	0.00
Lung	0.00	0.00	0.00	0.00	0.00	0.00
Heart	0.00	0.00	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00	0.00
Kidneys	0.00	0.00	0.00	0.00	0.00	0.00
Adrenals	0.00	0.00	0.00	0.00	0.00	0.00
Gonads	0.00	0.00	0.00	0.00	0.00	0.00
Muscle	0.00	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.00	0.00	0.00	0.00	0.00
Stomach. contents	0.00	0.00	0.00	0.00	0.00	0.00
Stomach	0.00	0.00	0.00	0.00	0.00	0.00
Gut contents	0.01	0.02	0.01	0.02	0.02	0.01
Gut	0.00	0.00	0.00	0.00	0.00	0.00
Liver	0.00	0.00	0.00	0.00	0.00	0.00
Carcass	0.21	0.52	0.63	1.03	0.60	0.34
Percentage absorbed	0.26	0.59	0.69	1.10	0.66	0.35
Surrounding skin	15.02	1.26	1.90	10.39	7.14	6.70
Protective cover	67.96	63.44	60.67	64.94	64.25	3.04
Application site	21.38	28.17	24.84	27.57	25.49	3.10
Skin wash	0.19	0.23	0.36	0.48	0.32	0.13
Total	104.81	93.69	88.46	104.48	97.86	8.12
Material absorbed						
in mg/animal	0.1146	0.2774	0.3244	0.5495	0.3165	0.1795
in mg/cm²	0.0115	0.0277	0.0324	0.0549	0.0316	0.0179

Table 6: Excretion and retention of radioactivity 120 h after a single dermal administration of ^{14}C-MDI to rats at a dose level of 4.0 mg/cm^2.
Single animal data and group mean values, results expressed as % of the radioactivity administered.

Animal No.	9	10	11	12	Mean	SD
Animal weight [g]	295.20	285.80	298.30	301.20	295.13	6.68
Specific acitvity [DPM/mg]	2140624	2140624	2140624	2140624	2140624	—
Dose admin. [mg/kg bw]	159.3	164.5	157.6	165.8	161.8	4.0
Dose admin. [mg/cm²]	4.701	4.701	4.701	4.995	4.775	0.147
Dose admin. [mg/animal]	47.01	47.01	47.01	49.95	47.75	1.47
Radioact. dose [MBq/animal]	1.68	1.68	1.68	1.78	1.71	0.05
Urine 0-8	0.01	0.01	0.01	0.01	0.01	0.00
Urine 8-24	0.02	0.02	0.02	0.02	0.02	0.00
Urine 24-48	0.01	0.01	0.01	0.01	0.01	0.00
Urine 48-72	0.01	0.01	0.01	0.01	0.01	0.00
Urine 72-96	0.00	0.00	0.00	0.00	0.00	0.00
Urine 96-120	0.00	0.00	0.00	0.00	0.00	0.00
Subtotal Urine	0.05	0.05	0.05	0.05	0.05	0.00
Feces 0-8	0.00	0.00	0.00	0.00	0.00	0.00
Feces 8-24	0.02	0.02	0.02	0.02	0.02	0.00
Feces 24-48	0.03	0.02	0.02	0.02	0.02	0.01
Feces 48-72	0.01	0.01	0.01	0.02	0.01	0.01
Feces 72-96	0.01	0.01	0.01	0.01	0.01	0.00
Feces 96-120	0.01	0.01	0.21	0.02	0.06	0.10
Subtotal Feces	0.08	0.07	0.27	0.09	0.13	0.10
Cage wash	0.02	0.00	0.00	0.08	0.03	0.04
Bloodcells	0.00	0.00	0.00	0.00	0.00	0.00
Plasma	0.00	0.00	0.00	0.00	0.00	0.00
Lung	0.00	0.00	0.00	0.00	0.00	0.00
Heart	0.00	0.00	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00	0.00
Kidneys	0.00	0.00	0.00	0.00	0.00	0.00
Adrenals	0.00	0.00	0.00	0.00	0.00	0.00
Gonads	0.00	0.00	0.00	0.00	0.00	0.00
Muscle	0.00	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.00	0.00	0.00	0.00	0.00
Stomach contents	0.00	0.00	0.00	0.70	0.18	0.35
Stomach	0.00	0.00	0.00	0.01	0.00	0.01
Gut contents	0.01	0.00	0.01	1.14	0.29	0.57
Gut	0.00	0.00	0.00	0.02	0.01	0.01
Liver	0.00	0.00	0.00	0.00	0.00	0.00
Carcass	0.34	0.03	0.34	0.11	0.21	0.16
Percentage absorbed	0.5	0.15	0.67	2.2	0.88	0.91
Surrounding skin	0.99	0.52	0.15	0.52	0.55	0.34
Protective cover	64.95	83.83	71.30	56.50	69.15	11.52
Application site	32.92	31.68	28.73	35.51	32.21	2.82
Skin wash	0.34	0.33	0.24	0.34	0.31	0.05
Total	99.70	116.51	101.09	95.07	103.09	9.31
Material absorbed						
in mg/animal	0.2351	0.0705	0.3150	1.0989	0.4299	0.4575
in mg/cm²	0.0235	0.0071	0.0315	0.1099	0.0430	0.0457

Table 7: Tissue concentrations of radioactivity 8, 24 and 120 h after a single dermal administration of ^{14}C-MDI to rats at a dose level of 4.0 mg/cm².
Single animal data and group mean values, results expressed as µg Eq/g.

Exposure time: 8 h	Sacrifice time: 8 h					
Animal No.	1	2	3	4	Mean	SD
Bloodcells	0.081	0.108	0.082	0.246	0.129	0.079
Plasma	0.150	0.231	0.143	0.272	0.199	0.063
Lung	0.099	0.124	0.087	0.125	0.109	0.019
Heart	0.055	0.076	0.056	0.090	0.069	0.017
Spleen	0.047	0.063	0.052	0.094	0.064	0.021
Kidneys	0.162	0.233	0.180	0.221	0.199	0.034
Adrenals	0.260	0.170	0.170	0.268	0.217	0.054
Gonads	0.037	0.060	0.040	0.053	0.048	0.011
Muscle	0.193	0.097	0.205	0.424	0.230	0.138
Brain	0.022	0.045	0.027	0.105	0.050	0.038
Adipose tissue	0.096	0.086	0.078	0.126	0.097	0.021
Bone	0.017	0.011	0.007	0.003	0.010	0.006
Thyroid	0.070	0.917	0.542	1.203	0.683	0.490
Pancreas	0.076	0.103	0.088	0.161	0.107	0.038
Liver	0.206	0.262	0.245	0.307	0.255	0.042
Carcass	0.459	0.802	0.569	0.277	0.527	0.219

Exposure time: 8 h	Sacrifice time: 24 h					
Animal No.	5	6	7	8	Mean	SD
Bloodcells	0.079	0.100	0.097	0.172	0.112	0.041
Plasma	0.195	1.443	0.190	0.438	0.567	0.596
Lung	0.071	0.089	0.097	0.165	0.106	0.041
Heart	0.048	0.046	0.059	0.083	0.059	0.017
Spleen	0.045	0.048	0.091	0.072	0.064	0.022
Kidneys	0.120	0.172	0.167	0.279	0.185	0.067
Adrenals	0.185	0.153	0.149	0.149	0.159	0.017
Gonads	0.051	0.033	0.067	0.066	0.054	0.016
Muscle	0.167	0.081	0.239	0.912	0.350	0.380
Brain	0.639	0.059	0.023	0.040	0.190	0.300
Adipose tissue	0.060	0.059	0.107	0.256	0.121	0.093
Bone	0.020	0.003	0.007	0.010	0.010	0.007
Thyroid	0.659	0.384	0.592	0.333	0.492	0.158
Pancreas	0.099	0.077	0.094	0.129	0.100	0.022
Liver	0.154	0.179	0.198	0.280	0.203	0.055
Carcass	0.660	1.558	2.106	3.709	2.008	1.281

Exposure time: 8 h	Sacrifice time: 120 h					
Animal No.	9	10	11	12	Mean	SD
Bloodcells	0.062	0.063	0.057	0.053	0.059	0.005
Plasma	0.098	0.071	0.111	0.089	0.092	0.017
Lung	0.079	0.037	0.062	0.061	0.060	0.017
Heart	0.034	0.026	0.088	0.027	0.044	0.029
Spleen	0.086	0.106	0.064	0.060	0.079	0.021
Kidneys	0.109	0.066	0.114	0.102	0.098	0.022
Adrenals	0.055	0.077	0.092	0.077	0.075	0.015
Gonads	0.124	0.053	0.042	0.028	0.062	0.043
Muscle	0.211	0.042	0.093	0.355	0.175	0.139
Brain	0.041	0.021	0.033	0.057	0.038	0.015
Adipose tissue	4.826*	0.111	0.089	0.192	0.131	0.054
Bone	0.000	0.000	0.000	0.001	0.000	0.001
Thyroid	0.677	0.557	0.460	0.280	0.494	0.168
Pancreas	0.122	0.122	0.079	0.095	0.105	0.021
Liver	0.092	0.065	0.094	0.091	0.086	0.014
Carcass	1.097	0.122	1.196	0.361	0.694	0.533

*: outlier; not used for statistics

Table 8: Excretion, retention and tissue concentration of radioactivity 8 h after a single dermal administration of ^{14}C-MDI to rats at a dose level of 0.4 mg/cm².
Single animal data and group mean values, results expressed as % of the radioactivity administered (excretion & retention) or ug Eq/g (tissue concentration).

Animal No.	13	14	15	16	Mean	SD
Animal weight [g]	296.50	300.30	282.90	273.70	288.35	12.30
Specific acitvity [DPM/mg]	30108408	30108408	30108408	30108408	30108408	—
Dose admin. [mg/kg bw]	13.8	13.7	14.5	16.2	14.6	1.2
Dose admin. [mg/cm²]	0.4105	0.4105	0.4105	0.4447	0.419	0.017
Dose admin. [mg/animal]	4.11	4.11	4.11	4.45	4.19	0.17
Radioact. dose [MBq/animal]	2.06	2.06	2.06	2.23	2.10	0.09
Urine 0-8	0.01	0.01	0.01	0.01	0.01	0.00
Subtotal Urine	0.01	0.01	0.01	0.01	0.01	0.00
Feces 0-8	0.00	0.00	0.00	0.00	0.00	0.00
Subtotal Feces	0.00	0.00	0.00	0.00	0.00	0.00
Cage wash	0.00	0.00	0.00	0.00	0.00	0.00
Plasma	0.00	0.00	0.00	0.00	0.00	0.00
Carcass	0.13	0.10	0.18	0.11	0.13	0.04
Percentage absorbed	0.14	0.11	0.19	0.12	0.14	0.04
Surrounding skin	1.55	2.37	1.47	7.29	3.17	2.78
Protective cover	41.35	40.73	37.00	58.88	44.49	9.78
Application site	57.11	49.61	70.19	40.11	54.26	12.70
Skin wash	0.59	0.87	0.97	0.82	0.81	0.16
Total	100.74	93.69	109.82	107.22	102.87	7.21
Material absorbed						
in mg/animal	0.0057	0.0045	0.0078	0.0053	0.0058	0.0014
in mg/cm²	0.00057	0.00045	0.00078	0.00053	0.00058	0.00014

Tissue concentration of radioactivity (in µg Eq/g)

Animal No.	13	14	15	16	Mean	SD
Plasma	0.017	0.019	0.030	0.020	0.022	0.006
Carcass	0.028	0.020	0.040	0.028	0.029	0.008

Table 9: Excretion, retention and tissue concentration of radioactivity 24 h after a single dermal administration of ^{14}C-MDI to rats at a dose level of 0.4 mg/cm². Single animal data and group mean values, results expressed as % of the radioactivity administered (excretion & retention) or ug Eq/g (tissue concentration).

Animal No.	17	18	19	20	Mean	SD
Animal weight [g]	300.40	297.00	283.90	294.60	293.98	7.13
Specific acitvity [DPM/mg]	30108408	30108408	30108408	30108408	30108408	—
Dose admin. [mg/kg bw]	13.7	13.8	15.7	13.9	14.3	1.0
Dose admin. [mg/cm²]	0.4105	0.4105	0.4447	0.4105	0.419	0.017
Dose admin. [mg/animal]	4.11	4.11	4.45	4.11	4.19	0.17
Radioact. dose [MBq/animal]	2.06	2.06	2.23	2.06	2.10	0.09
Urine 0-8	0.01	0.02	0.01	0.01	0.01	0.01
Urine 8-24	0.02	0.04	0.03	0.03	0.03	0.01
Subtotal Urine	0.03	0.06	0.04	0.04	0.04	0.01
Feces 0-8	0.01	0.01	0.02	0.00	0.01	0.01
Feces 8-24	0.02	0.05	0.03	0.04	0.04	0.01
Subtotal Feces	0.03	0.06	0.05	0.04	0.05	0.01
Cage wash	0.01	0.01	0.00	0.01	0.01	0.01
Plasma	0.00	0.00	0.00	0.00	0.00	0.00
Carcass	0.11	0.06	0.24	0.12	0.13	0.08
Percentage absorbed	0.18	0.19	0.33	0.21	0.23	0.07
Surrounding skin	0.34	0.16	1.75	3.22	1.37	1.43
Protective cover	51.97	28.90	63.20	56.06	50.03	14.83
Application site	57.43	73.34	43.72	48.00	55.62	13.13
Skin wash	0.55	0.95	0.63	1.13	0.82	0.27
Total	110.47	103.54	109.63	108.62	108.07	3.11
Material absorbed						
in mg/animal	0.0074	0.0078	0.0147	0.0086	0.0096	0.0034
in mg/cm²	0.00074	0.00078	0.00147	0.00086	0.00096	0.00034

Tissue concentration of radioactivity (in µg Eq/g)

Animal No.	17	18	19	20	Mean	SD
Plasma	0.018	0.036	0.023	0.027	0.026	0.008
Carcass	0.025	0.014	0.062	0.028	0.032	0.021

Table 10: Excretion, retention and tissue concentration of radioactivity 120 h after a single dermal administration of ^{14}C-MDI to rats at a dose level of 0.4 mg/cm². Single animal data and group mean values, results expressed as % of the radioactivity administered (excretion & retention) or ug Eq/g (tissue concentration).

Animal No.	21	22	23	24	Mean	SD
Animal weight [g]	288.40	290.90	268.00	281.20	282.13	10.28
Specific acitvity [DPM/mg]	30108408	30108408	30108408	30108408	30108408	—
Dose admin. [mg/kg bw]	13.0	15.3	15.3	15.8	14.9	1.3
Dose admin. [mg/cm²]	0.3763	0.4447	0.4105	0.4447	0.419	0.033
Dose admin. [mg/animal]	3.76	4.45	4.11	4.45	4.19	0.33
Radioact. dose [MBq/animal]	1.89	2.23	2.06	2.23	2.10	0.16
Urine 0-8	0.02	0.01	0.02	0.01	0.02	0.01
Urine 8-24	0.02	0.02	0.02	0.01	0.02	0.01
Urine 24-48	0.02	0.02	0.03	0.02	0.02	0.01
Urine 48-72	0.01	0.01	0.02	0.01	0.01	0.01
Urine 72-96	0.04	0.01	0.01	0.00	0.02	0.02
Urine 96-120	0.01	0.01	0.01	0.00	0.01	0.01
Subtotal Urine	0.12	0.08	0.11	0.05	0.09	0.03
Feces 0-8	0.03	0.01	0.01	0.00	0.01	0.01
Feces 8-24	0.03	0.00	0.01	0.01	0.01	0.01
Feces 24-48	0.04	0.04	0.06	0.05	0.05	0.01
Feces 48-72	0.04	0.04	0.05	0.02	0.04	0.01
Feces 72-96	0.02	0.02	0.04	0.02	0.03	0.01
Feces 96-120	0.04	0.02	0.02	0.02	0.03	0.01
Subtotal Feces	0.20	0.13	0.19	0.12	0.16	0.04
Cage wash	0.05	0.18	0.01	0.01	0.06	0.08
Plasma	0.00	0.00	0.00	0.00	0.00	0.00
Caracass	0.34	0.70	0.36	0.12	0.38	0.24
Percentage absorbed	0.71	1.09	0.67	0.30	0.69	0.32
Surrounding skin	2.23	0.20	1.72	1.73	1.47	0.88
Protective cover	39.66	25.01	51.57	54.31	42.64	13.36
Application site	59.66	63.64	59.15	57.10	61.14	5.12
Skin wash	0.53	0.43	0.57	0.35	0.47	0.10
Total	102.79	95.37	113.68	113.79	106.41	8.99
Material absorbed						
in mg/animal	0.0267	0.0485	0.0275	0.0133	0.0290	0.0145
in mg/cm²	0.00267	0.00485	0.00275	0.00133	0.00290	0.00145

Tissue concentration of radioactivity (in µg Eq/g)

Animal No.	21	22	23	24	Mean	SD
Plasma	0.015	0.012	0.020	0.003	0.014	0.005
Carcass	0.081	0.190	0.093	0.030	0.099	0.067

Table 11: Excretion and retention of radioactivity 120 h after a single intradermal administration of ^{14}C-MDI to rats at a dose level of 0.4 mg/animal.
Single animal data and group mean values, results expressed as % of the radioactivity administered.

Animal No.	31	32	33	34	Mean	SD
Animal weight [g]	267.23	252.00	306.65	308.24	283.03	27.74
Specific activity [DPM/mg]	101465872	101465872	101465872	101465872	1.01e+08	---
Dose admin. [mg/kg bw]	1.7	1.8	1.8	1.9	1.8	0.1
Dose admin. [mg/animal]	0.460	0.460	0.550	0.590	0.515	0.066
Radioact. dose [MBq/animal]	0.78	0.78	0.92	0.99	0.87	0.11
Urine 0-8	0.47	0.29	0.25	0.34	0.34	0.10
Urine 8-24	0.82	0.99	0.88	0.69	0.85	0.13
Urine 24-48	1.34	1.32	0.67	0.88	1.05	0.33
Urine 48-72	0.88	1.10	0.86	0.45	0.82	0.27
Urine 72-96	0.33	0.55	0.58	0.26	0.43	0.16
Urine 96-120	1.06	1.51	0.86	0.66	1.02	0.36
Subtotal Urine	4.90	5.76	4.10	3.28	4.51	1.06
Feces 0-8	1.16	0.06	0.03	0.01	0.32	0.56
Feces 8-24	4.01	2.97	1.50	10.62	4.78	4.03
Feces 24-48	5.25	5.51	3.11	7.73	5.40	1.89
Feces 48-72	2.84	2.83	2.22	2.05	2.49	0.41
Feces 72-96	1.52	2.57	1.80	1.42	1.83	0.52
Feces 96-120	2.26	2.60	1.89	2.35	2.28	0.29
Subtotal Feces	17.04	16.54	10.55	24.18	17.08	5.58
Cage wash	0.81	0.98	0.19	1.03	0.75	0.39
Bloodcells	0.04	0.06	0.04	0.02	0.04	0.02
Plasma	0.21	0.23	0.20	0.11	0.19	0.05
Lung	0.02	0.05	0.03	0.01	0.03	0.02
Heart	0.01	0.02	0.01	0.01	0.01	0.01
Spleen	0.01	0.01	0.01	0.00	0.01	0.01
Kidneys	0.07	0.09	0.09	0.04	0.07	0.02
Adrenals	0.00	0.00	0.00	0.00	0.00	0.00
Gonads	0.04	0.05	0.04	0.02	0.04	0.01
Muscle	0.01	0.01	0.01	0.00	0.01	0.01
Brain	0.00	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.01	0.01	0.00	0.01	0.01
Stomach contents	0.07	0.02	0.01	0.09	0.05	0.04
Stomach	0.03	0.03	0.01	0.01	0.02	0.01
Gut contents	0.35	0.35	0.39	0.81	0.48	0.22
Gut	0.06	0.11	0.14	0.06	0.09	0.04
Liver	0.31	0.38	0.40	0.18	0.32	0.10
Carcass	2.00	3.64	2.01	1.07	2.18	1.07
Percentage absorbed	25.98	28.34	18.24	30.92	25.87	5.47
Surrounding skin	23.89	4.63	3.21	2.14	8.47	10.33
Application site	47.39	71.93	79.93	66.54	66.45	13.84
Skin wash	0.07	0.21	0.03	0.14	0.11	0.08
Total	97.33	105.11	101.41	99.74	100.90	3.27
Material absorbed in mg/animal	0.1195	0.1304	0.1003	0.1824	0.1332	0.0351

Table 12: Tissue concentration of radioactivity 120 h after a single intradermal administration of ^{14}C-MDI to rats at a dose level of 0.4 mg/animal.
Single animal data and group mean values, results expressed as ug Eq/g.

Animal No.	31	32	33	34	Mean	SD
Bloodcells	0.114	0.173	0.158	0.058	0.126	0.052
Plasma	0.275	0.371	0.382	0.170	0.300	0.099
Lung	0.102	0.155	0.136	0.057	0.113	0.043
Heart	0.070	0.097	0.066	0.035	0.067	0.025
Spleen	0.090	0.127	0.124	0.054	0.099	0.034
Kidneys	0.180	0.231	0.242	0.120	0.193	0.056
Adrenals	0.086	0.157	0.115	0.052	0.103	0.045
Gonads	0.070	0.081	0.076	0.032	0.065	0.022
Muscle	0.025	0.029	0.024	0.012	0.023	0.007
Brain	0.006	0.009	0.006	0.004	0.006	0.002
Adipose tissue	0.033	0.039	0.037	0.017	0.032	0.010
Bone	0.042	0.057	0.043	0.030	0.043	0.011
Thyroid	0.089	0.098	0.091	0.043	0.080	0.025
Pancreas	0.037	0.055	0.058	0.025	0.044	0.016
Liver	0.141	0.177	0.205	0.102	0.156	0.045
Carcass	0.071	0.132	0.075	0.042	0.080	0.038

7 LIST OF ABBREVIATIONS

%	percent
appl.	application
bw	body weight
cm	centimeter
DPM	disintegrations per minute
Eq	equivalents
g	gram
h	hour
LSC	liquid scintillation counter
MBq	Mega-Bequerel
mg	milligram
M	molar
SD	standard deviation
µg	microgram

8 APPENDIX

- Purity Statements of the radiolabelled test substances (I A 001; I A 002)
- Sample HPLC-chromatogram (purity check; I A 003)

I A 001

BASF Aktiengesellschaft

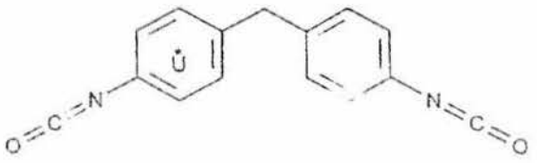
BASF

01B0431/946010

Drug Technologies
Isotope Laboratory
67056 Ludwigshafen, Germany

Test Facility: BASF Aktiengesellschaft - Ecology and Environmental Analytics - Box 120 - 67114 Limburgerhof

Purity Statement / Product Specification

Reg.-No.: ———	BAS-No.: ———	Batch-No.: 588-02
Study Code: ———	CAS-No.:	
Molecular formula:	$C_{15}H_{10}N_2O_2$	Molecular mass: 251.1 g/mol
Chemical name:	4,4'-Methylenebis-[ring-U-^{14}C]-phenylisocyanate	
Structural formula:		
Specific activity:	4.1 MBq/mg (Amersham) 246000 dpm/µg	Date: September 21, 1992
Radiochemical purity:	> 95 %	Date: December 20, 1995
Chemical purity:	———	Date: ———
Analytical methods:	Radio-HPLC	
Impurities:	Not known	
Stability:	Not known	
Storage:	At low temperature and in the dark	
Note:	Dispatch of 46.3 mg (190 MBq) to BASF AG, ZHT/ES (Dr. Leibold)	

Date: July 8, 1996

July 8 1996
Date

Signature

BASF Aktiengesellschaft 0180431/946010

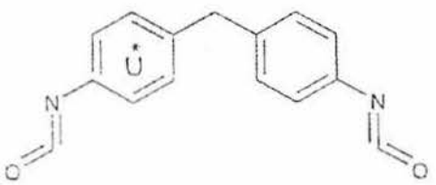
ZHV - Pilot plants and Physicochemical Methods for Life Sciences
Isotope Laboratory
67056 Ludwigshafen, Germany

Test Facility: BASF Aktiengesellschaft - Ecology and Environmental Analytics - Box 120 - 67114 Limburgerhof

Purity Statement / Product Specification

Reg.-No.: —	**BAS-No.:** —	**Batch-No.:** 588-1201
Study Code: PI970038	**CAS-No.:**	**Label:** ring-U-^{14}C
Molecular formula: $C_{15}H_{10}N_2O_2$	**Molecular mass:** 250.2 g/mol (unlabelled)	
Chemical name:	4,4'-Methylenebis-([ring-U-^{14}C]-phenylisocyanate)	

Structural formula:



Specific activity:	3.55 MBq/mg (by LSC) 213000 dpm/µg	**Date:** December 12, 1997
Radiochemical purity:	> 99 % (by Radio-HPLC)	**Date: Date:** December 10, 1997
Analytical methods:	LSC and Radio HPLC	
Stability:	Not known	
Storage:	At low temperature and in the dark	
Note:	Dispatch of 20.7 mg (73,5 MBq) to ZHT/ES, BASF AG, Dr. Leibold	**Date:** December 10, 1997

Dec. 12, 1997
Date

Signature

Study is performed in compliance with the GLP rules unless stated otherwise.

I A 003

01B0431/946010

Ans. 2621D2, LSC 1/2

Ausw.Datum: 97/Jan/10 ##Ans.262102,LSC1/2

Pfad :C:\HLABE Param.ID : MDI berthold HPLC-Program 1.65 30.Apr.92

Datum der Messung : 97/Apr/30 08:44 Dwell time = 4s Messzeit = 9m00s

Fluss-Rate = 1.20[ml/min] Zellvolumen = 0.40ml LL = 25 UL = 750 R.T. Abweichung = 20s

Verz. = 14-C : 12s

30.4.97 Ch

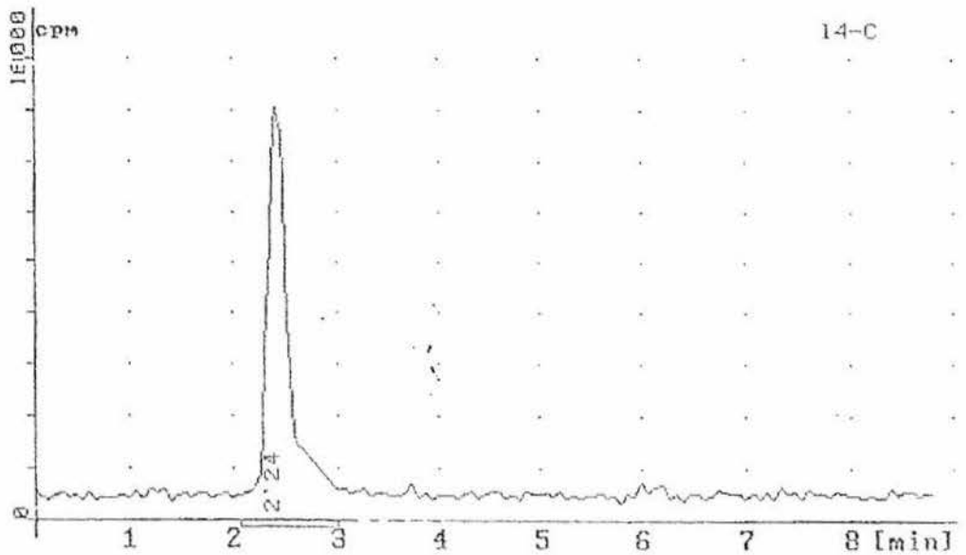
Schott-grün

01B0431/946010 MDI
Ans.262102,30.04.97

#	Name der ROIs	R.t.	14-C [cts]	% ROI	% all
1	MDI	2m24s	4035.0	100.0	36.7

Brutto :		11162.0
Netto :		10982.0
Brutto in ROI :		4055.0
Netto in ROI :		4035.0
Background :		BG 20 [cpm]

Ans.2621D2,LSC1/2 97/Apr/30 08:44



D 05

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